**UNITED STATES PATENT AND TRADEMARK OFFICE**

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**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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*Ex parte* JAMES H. PICKAR

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Appeal 2006-3012
Application 09/808,878
Technology Center 1600

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HEARD December 14, 2006

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Before MILLS, GRIMES, and LINCK, *Administrative Patent Judges.*

GRIMES, *Administrative Patent Judge.*

DECISION ON APPEAL

This appeal involves claims to a hormone replacement therapy for menopausal women, which the examiner has rejected as obvious. We have jurisdiction under 35 U.S.C. § 134. We affirm.

BACKGROUND

As "estrogens decline during the time preceding (perimenopause) and following the menopause (postmenopause), various physiological changes may result, including . . . vasomotor instability manifested as hot flushes."

(Specification 1.) "Estrogen replacement therapy (ERT) is beneficial for symptomatic relief of hot flushes." (*Id.* at 2.)

ERT may increase the relative risk of endometrial cancer. (*Id.* at 3.) "There are extensive clinical data showing that the relative risk of endometrial cancer can be reduced by the addition of a progestin, either sequentially or continuously." (*Id.* at 4.) "Continuous combined hormone replacement therapy (HRT) . . . has been shown to be effective in relieving . . . vasomotor symptoms." (*Id.*) PREMPRO is a commercially available combination HRT product (*id.*) that contains 0.625 mg of conjugated equine estrogens USP and 2.5 mg of medroxyprogesterone acetate (MPA) (*id.* at 5).

The specification discloses that administering either 0.45 mg or 0.3 mg of conjugated equine estrogens (a.k.a. PREMARIN) in combination with 1.5 mg of MPA "reduce[s] the number and severity of hot flushes to the same extent as the higher dose combination containing 0.625 mg PREMARIN plus 2.5 mg MPA." (*Id.* at 9-10.) The specification characterizes this result as unexpected. (*Id.* at 9, line 32.)

## DISCUSSION

### 1. CLAIMS

Claims 7, 11, 12, and 69 are pending and on appeal. Claim 7, the only independent claim, reads as follows:

> 7. A method of treating or inhibiting vasomotor symptoms in a perimenopausal, menopausal, or postmenopausal woman in need thereof, which comprises orally providing to said woman continuously and uninterruptedly over the treatment period, a combination of conjugated estrogens, USP and a daily dosage of about 1.5 mg of medroxyprogesterone acetate, wherein the daily dosage of conjugated equine estrogens is between about 0.45 mg and about 0.3 mg.

Appellant has not argued the claims separately. Therefore, claims 11, 12, and 69 will stand or fall with claim 7. 37 CFR § 41.37(c)(1)(vii).

Claim 7 is directed to a method of hormone replacement therapy. The claimed method comprises administering a daily dosage of about 1.5 mg of MPA and about 0.3 to 0.45 mg of conjugated equine estrogens "continuously and uninterruptedly over the treatment period." The specification defines "continuous and uninterrupted" to mean at least once-daily administration with no break in the treatment regimen during the treatment period. Page 7, lines 29-32.

2. OBVIOUSNESS

Claims 7, 11, 12, and 69 stand rejected under 35 U.S.C. § 103 as obvious in view of Plunkett.[1] The Examiner reasons that Plunkett "teaches a method of treating hot flashes comprising administering continuously and uninterruptedly both progestogen and estrogen in daily dosage units." (Answer, page 3.) The Examiner points out that Plunkett teaches the specific combination of MPA and conjugated equine estrogens (CEE) and teaches dosage ranges of 0.3 to 2.5 mg/day for CEE and 1 to 15 mg/day for MPA. (*Id.*) The Examiner also characterizes as "preferred" Plunkett's disclosed dosages of 1 to 2.5 mg/day of MPA and 0.300 to 0.600 mg/day of CEE. (*Id.*, citing "claims 34-35 [sic, 32 and 35].")

The Examiner acknowledges that Plunkett does not teach the specific dosage combination recited in the instant claims, but concludes:

> One of ordinary skill in the art would have been motivated to employ conjugated equine estrogen/medroxyprogesterone in the

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[1] Plunkett et al., Re. 36,247, issued Jul. 6, 1999.

> specific dosages claimed herein in a method of treating hot flashes because they (dosages herein) fall within the therapeutic ranges of the conjugated equine estrogen/medroxyprogesterone taught by the prior art. Optimization of amounts is within the purview of the Skilled Artisan, and is therefore obvious absent evidence to the contrary.

(*Id.* at 4.)

We agree with the Examiner that Plunkett's teachings would have made the method of claim 7 prima facie obvious. Plunkett does not specifically disclose a method of controlling hot flushes by administering 1.5 mg/day of MPA in combination with 0.3 to 0.45 mg/day of CEE. However, Plunkett teaches a method of controlling hot flushes (col. 3, ll. 51-53) by "continuously and uninterruptedly administering a progestogen and an estrogen" (col. 3, ll. 8-9). One "especially preferred combination[ ]" is conjugated equine estrogen and medroxyprogesterone acetate (col. 6, l. 53; col. 7, ll. 10-11), the same compounds recited in claim 7.

Plunkett discloses dosages of conjugated equine estrogens ranging from a minimum of 0.300 mg/day to a maximum of 2.5 mg/day; 0.600 mg/day is disclosed as preferred (col. 4, l. 65). Plunkett discloses dosages of MPA ranging from a minimum of 1 mg/day to a maximum of 15 mg/day; 2.5 mg/day is disclosed as preferred (col. 5, l. 50). Plunkett claims methods involving administering less than the "preferred dosage" of MPA or conjugated equine estrogens. See claim 32 (about 1 to about 2.5 mg/day MPA); claim 35 (about 0.300 to about 0.600 mg/day CEE); and claim 42 (about 2.5 mg/day MPA and about 0.300 mg/day CEE). Thus, Plunkett discloses dosage ranges for those compounds that encompass the dosages

recited in claim 7 and teaches specific dosage ranges that are less than the disclosed "preferred" dosages.

Finally, Plunkett teaches that patients should be given only as much hormone as necessary to achieve the desired result (col. 4, ll. 1-5):

> The actual unit dosages are selected according to conventionally known methods, e.g. body weight of patient and biological activity of the hormones, with the ultimate goal of producing the desired result with the minimum quantities of hormones.

Thus, Plunkett directs those skilled in the art to use the minimum dosage needed to produce the desired effect. We agree with the examiner that these teachings would have suggested to those of ordinary skill in the art a method of treating hot flushes by continuously administering about 1.5 mg/day of MPA in combination with about 0.3 to 0.45 mg/day of CEE; i.e., the method recited in claim 7.

Appellant argues that Plunkett "does not provide any suggestion or motivation to use the claimed lower dosage amount of CEE and MPA." (Br. 6.) Appellant also argues that "one skilled in the art would have to perform undue experimentation to arrive at Appellant's particular low dose combination among the vast possibilities contemplated by Plunkett." (*Id.* at 7.) Along the same line, Appellant argues that those skilled in the art would not have been led to optimize the dosages in Plunkett's method because "in designating the preferred amounts, Plunkett et al. taught that those particular amounts *were* the optimal amounts." (Reply Br., page 3.)

This argument is not persuasive. While Plunkett discloses that a variety of estrogens and progestogens would be suitable for use in the disclosed method, it describes the specific combination of CEE and MPA as

especially preferred. It also provides specific dosage ranges for both CEE and MPA, and the disclosed dosage ranges encompass the dosages recited in claim 7. Finally, Plunkett directs the skilled artisan to the lower part of the disclosed dosage ranges, in its direction to use the minimum amount of hormones necessary to produce the desired result (col. 4, ll. 1-5) and in its description of specific dosage ranges that are less than the disclosed "preferred" dosages (claims 32, 35, and 42).

We do not agree with Appellant that those skilled in the art would have considered Plunkett's "preferred" dosages to be the optimal dosages. Plunkett discloses a range of dosages for each hormone to be used in the disclosed method and teaches that the actual dosages are selected according to conventional methods, based on factors including the body weight of the patient and the biological activity of the hormone. Plunkett specifically claims methods that comprise administering less than the "preferred" dosages of both MPA (claim 32) and CEE (claims 34 and 42). Thus, we do not agree with Appellant's implicit assertion that the only dosage disclosed by Plunkett that those skilled in the art would have found obvious to use is the single dosage described as "preferred."

Appellant also argues that those skilled in the art would have understood from Plunkett that the "preferred" dosages were thought to be the minimum effective doses. (Reply Br. 4-5.) Appellant cites the Second Lobo Declaration as providing evidence that the preferred dosages disclosed by Plunkett would have been considered the minimum effective dosages. (Br. 8-9; Reply Br. 4-5.) Appellant argues that "[a]ccordingly, the teachings of the prior art and the knowledge generally available in the art would not have

suggested to those skilled in the art that the use of 1.5 mg MPA in combination with about 0.3 to about 0.45 mg CEE would have been reasonably successful in providing relief of vasomotor symptoms of menopause." (Br. 8.)

The evidence of record does not support Appellant's position that those skilled in the art would have expected the lower dosages of MPA and CEE disclosed by Plunkett to be unsuccessful in controlling hot flushes. The Second Lobo Declaration does not support the weight Appellant puts on it. In that declaration, Dr. Lobo declares that "[f]or the past 20 years, the dosage of 0.625 mg CEE has been accepted as the minimum dosage of estrogen necessary to relieve the symptoms of menopause, including hot flushes and bone loss." ¶ 2. As support for this statement, Dr. Lobo cites Sobel[2] and Kronenberg.[3] These references, however, do not state that 0.625 mg/day of CEE was accepted as the minimum effective dosage.

Sobel states that the *standard* dose of conjugated estrogens was 0.625 mg (page 313). Kronenberg states that the "*most commonly used* regimen for treating hot flashes in the United States is 0.625 to 1.25 mg of oral conjugated equine estrogens (Premarin)" (page 109, emphasis added). A dose that is "standard" or a regimen that is "most commonly used," however, is not necessarily the same as a dosage or regimen that is considered the minimum effective dose. Rather, a standard or most

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[2] Sobel, "Progestins in preventative hormone therapy," *Obstetrics and Gynecology Clinics of North America*, Vol. 21, No. 2, pp. 299-319 (1994).
[3] Kronenberg, "Chap. 9 Hot Flashes," in Treatment of the Postmenopausal Woman: Basic and Clinical Aspects, R.A. Lobo (ed.), Raven Press, NY, pp. 97-117 (1994).

commonly used dosage represents a commercially marketed product that is designed to be administered to many patients. A dosage intended for administration to many patients would necessarily contain a dosage that is large enough to be effective in a large majority of patients but not so much as to cause side effects or complications in a significant number. As taught by Plunkett, the minimum effective dosage is determined patient-by-patient and depends on factors including the body weight of an individual patient.

In addition, the method of claim 7 only requires administration of CEE and MPA to control hot flushes ("vaosmotor symptoms"). Dr. Lobo's declaration, by contrast, addresses the amount of hormones allegedly thought necessary "to relieve the symptoms of menopause, including hot flushes *and bone loss*." ¶ 2. The amount of hormones required to alleviate hot flushes is not necessarily the same as the amount required to alleviate all of the symptoms of menopause, including bone loss.

Finally, the evidence of record includes Utian.[4] Utian states that "[n]umerous small studies of short duration have found lower doses of various estrogens to be effective in reducing the number and severity of hot flushes, the effect being almost as great as that seen with the most commonly prescribed HRT doses." (Page 1066, left-hand column.) Utian was published after the effective filing date asserted for the present application but cites at least three prior art references in support of the quoted statement.

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[4] Utian et al., "Relief of vasomotor symptoms and vaginal atrophy with lower doses of conjugated equine estrogens and medroxyprogesterone acetate," *Fertility and Sterility*, Vol. 75, p. 1065-1079 (2001). The co-authors of Utian include inventor James H. Pickar.

In summary, after considering all of the evidence of record, we find that the weight of the evidence does not support Dr. Lobo's assertion that 0.625 mg/day of CEE was considered the minimum daily dosage required to control hot flushes at the time the claimed method was made.

Dr. Lobo also states that the "dosage of 2.5 mg of MPA has been recognized as the minimum amount needed to oppose 0.625 mg CEE and protect the endometrium." ¶ 2. No evidence is cited to support this assertion but regardless of its accuracy, Dr. Lobo's declaration does not address what dosages of MPA would have been expected to be necessary to oppose CEE at the lower dosages suggested by Plunkett – 0.3 to 0.6 mg/day.

Appellant also asserts that he has provided evidence of unexpected results to rebut any prima facie case of obviousness. (Br. 9-12; Reply Br. 5-8.) Appellant points to Dr. Lobo's discussion of the "Women's Health, Osteoporosis, Progestin, Estrogen (H.O.P.E.)" study and the results of that study that are reproduced in the instant specification. In his first declaration, Dr. Lobo states:

> I and others expected that the study would show that there would be a dose response such that the lower combination doses of CEE and MPA would have some effect in reducing the number and severity of hot flushes compared with the placebo, but far less of an effect than the standard dose of CEE 0.625 [mg] plus 2.5 mg MPA. In fact, I and others were interested in seeing the results of the various lower doses, but doubted the study was worth the economic effort.

(First Lobo Declaration, ¶ 12.) Dr. Lobo states that "[i]t was very surprising and unexpected" that a daily dosage of 1.5 mg MPA combined with 0.3 or

0.45 mg CEE reduced the number and severity of hot flushes to the same extent as 2.5 mg MPA combined with 0.625 mg CEE. (*Id.* at ¶ 14.)

We do not find Dr. Lobo's declarations to outweigh the evidence of obviousness. Dr. Lobo's statements may reflect his own state of mind, but the determination of obviousness is not based on the expectations of any single individual.[5] Rather, obviousness under § 103 is determined based on the expectations of a hypothetical person of ordinary skill in the art fully aware of the state of the prior art. *See In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998) ("Obviousness is determined from the vantage point of a hypothetical person having ordinary skill in the art to which the patent pertains. . . . The legal construct also presumes that all prior art references are available to this hypothetical skilled artisan.").

Here, the evidence of record shows that such a person would not have found the results shown in the specification to be unexpected. Utian reports the results of the HOPE study. The results shown in Utian's Figure 1B and Figure 3B appear to correspond to those shown in the instant specification, page 9, lines 15-20 and 20-25, respectively. Utian states that the results of the HOPE study "showed that lower-dosage combinations of CEE and CEE/MPA were effective in decreasing the number and severity of hot flushes. . . . In general, the lower-dosage combinations, especially CEE 0.45/MPA 1.5 and CEE 0.3/MPA 1.5, were as effective for symptom relief

[5] We do not find credible Dr. Lobo's statement that his expectations were shared by "others" because Appellant has provided no evidence to support that statement.

as the most commonly prescribed dosage combination of CEE and MPA." (Page 1073, right-hand column.)

Importantly, Utian expresses no surprise at this result: "These findings are *consistent with results of previous studies* that examined the efficacy of lower estrogen dosages for relief of vasomotor symptoms. . . . The results reported here are especially relevant because they *confirm* the effectiveness of lower doses of CEE and MPA . . . in the context of a large clinical trial." (Paragraph bridging pages 1073 and 1074, emphases added.)

Thus, Utian provides evidence that a person of ordinary skill in the art in the field of hormone replacement therapy would have been aware of "numerous small studies" showing that low doses of estrogen had been shown to be effective in treating hot flushes. Utian also provides evidence that a person of ordinary skill in the art would have found the results of the HOPE study – and the results reported in the instant specification – to be not unexpected but "consistent with results of previous studies"; in other words, expected.

Appellant also argues that "the H.O.P.E. study further unexpectedly showed an additive effect of MPA at low doses." (Br. 10, citing the First Lobo Declaration.) In that declaration, Dr. Lobo declares that the "H.O.P.E. study demonstrated that dosages of CEE and MPA may be better than equivalent dosages of unopposed CEE for vasomotor symptom relief." ¶ 15. This result is said to be unexpected because "[p]revious studies with various dosages of CEE showed no additive effect of MPA on vasomotor relief." *Id.*

(citing Greendale[6]). Thus, Dr. Lobo declares that the "H.O.P.E. study surprisingly demonstrated that at these low doses [1.5 mg MPA plus 0.3 or 0.45 mg CEE] MPA may contribute to ameliorating the vasomotor symptoms." *Id.*

We do not find the additive effect of MPA on vasomotor symptoms, in combination with low doses of estrogen, to overcome the prima facie case of obviousness. It is true that Greendale reports that MPA does not contribute to reducing vasomotor symptoms when administered in combination with 0.625 mg of CEE. See, e.g., page 986, last paragraph. It is also true that Utian reports that the results of the HOPE study "suggest that lower doses of CEE combined with MPA may be better than equivalent lower doses of unopposed CEE for vasomotor symptom relief." Page 1074, left-hand column. Thus, this result of the HOPE study might well have been unexpected in comparison to the earlier PEPI study reported by Greendale.

Unexpected results, however, must be established in comparison to the closest prior art. *See In re Baxter-Travenol Labs.*, 952 F.2d 388, 392, 21 USPQ2d 1281, 1285 (Fed. Cir. 1991).

Here, Greendale is not the closest prior art. The embodiment in the prior art that is closest to the claimed method is that of Plunkett's claim 42: 2.5 mg of MPA combined with 0.3 mg of CEE. Thus, the relevant question is *not* whether the combination of claim 7 (1.5 mg MPA and 0.3 - 0.45 mg CEE) is unexpectedly superior to 0.3 - 0.45 mg CEE alone. The relevant

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[6] Greendale et al., "Symptom relief and side effects of postmenopausal hormones: Results from the Postmenopausal Estrogen/Progestin Interventions Trial," *Obstetrics & Gynecology*, Vol. 92, pp. 982-988 (1998).

question is whether the combination of claim 7 is unexpectedly superior to the prior art combination of 2.5 mg MPA and 0.3 mg CEE. Appellant's evidence provides no comparison to the closest prior art and therefore shows no unexpected properties compared to the closest prior art.

SUMMARY

The reference relied on by the examiner shows that claim 7 would have been prima facie obvious to those of ordinary skill in the art. Appellant's evidence does not outweigh the evidence of obviousness. We affirm the rejection of claim 7. Claims 11, 12, and 69 fall with claim 7.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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